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RESEARCH PAPER



Cost-effectiveness analysis of different seasonal influenza vaccines in the elderly Italian population

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ABSTRACT

In the perspective of reaching at least 75% influenza vaccination coverage in the elderly and substantial budget constraints, Italian decision makers are facing important challenges in determining an optimal immunization strategy for this growing and particularly vulnerable population. Four different influenza vaccines are currently available for Italian older adults aged 65 years or above, namely trivalent inactivated vaccines (TIVs), MF59-adjuvanted TIV (MF59-TIV), intradermal TIV (ID-TIV) and quadrivalent inactivated vaccines (QIVs). The present study is the first to compare the cost-effectiveness profiles of virtually all possible public health strategies, including the aforementioned four vaccine formulations as well non-vaccination. For this purpose, a decision tree model was built *ex novo*; the analysis was conducted from the third-payer perspective in the timeframe of one year. All available vaccines were cost-effective compared with non-vaccination. However, MF59-TIV had the most favorable economic profile in the Italian elderly population. Indeed, compared with non-vaccination, it was deemed highly cost-effective with an incremental cost-effectiveness ratio (ICER) of €10,750 per quality-adjusted life year (QALY). The ICER was much lower (€4,527/QALY) when MF59-TIV was directly compared with TIV. ID-TIV and QIV were dominated by MF59-TIV as the former comparators were associated with greater total costs and lower health benefits. Both deterministic and probabilistic sensitivity analyses confirmed robustness of the base case results. From the economic perspective, MF59-TIV should be considered as a preferential choice for Italian older adults aged 65 years or above.

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Introduction

Every season influenza affects 10–20% of the population.¹ Influenza attack rate is usually significantly higher in children and adolescents; however, most hospitalizations and about 90% of influenza-attributable deaths, which may be considered as major cost drivers, occur among older adults aged ≥ 65 years.² Annual influenza vaccination remains the primary public health measure able to prevent infection, diminish influenza-associated complications, hospitalizations and deaths and thus, reduce the burden of disease;³ this is the reason why virtually all industrialized and many developing countries recommend the annual vaccination for the elderly and other high-risks groups.^{4,5} Despite this, vaccination coverage (VC) among the elderly persists at relatively low levels in most countries.⁴

It is well-recognized that, compared with non-vaccination, annual influenza immunization is cost-effective or even cost-saving in different settings and population groups including the elderly (For a review, see⁶). However, the landscape of available influenza vaccines is changing continuously. For instance, in Italy four different types of vaccine are currently commercially available and indicated for immunization of the elderly: trivalent inactivated vaccines (TIVs), MF59-adjuvanted TIV (MF59-TIV), intradermal TIV (ID-TIV) and quadrivalent inactivated vaccines

(QIVs). These vaccines differ in several aspects including manufacturing processes, contents, route of administration, strain coverage, and vaccine effectiveness (VE).^{7,8}

Among the aforementioned vaccine formulations, MF59-TIV was the first specifically designed to overcome the phenomenon of immunosenescence.⁹ First licensed in 1997 in Italy, MF59-TIV has consistently been shown to be superior to traditional vaccines in terms of immunogenicity and field effectiveness in tens of clinical trials and observational studies (For reviews, see refs. 10–13). Twenty years of widespread use in the general population, regulatory approval in approximately 30 countries, and several economic evaluations,^{14–20} have all established a favorable economic profile of MF59-TIV.

Given the objective to reach at least 75% influenza VC in the elderly,²¹ the steady increasing size of the elderly population,²² issues around the vaccine hesitancy,²³ the increasing financial pressure on the public health sector²⁴ and the ready availability of four different vaccines, Italian decision makers are facing significant challenges in defining an optimal immunization strategy. Existing Italian economic evaluations do not precisely reflect the current market situation, in that the previous elderly-specific research compared few options. The economic evaluations of all possible strategies may undoubtedly aid or

even guide critical decisions; in this view, the present study aimed to compare all seasonal influenza vaccines available in Italy for immunization of the elderly in terms of cost-effectiveness (CE).

Results

Base case

Table 1 shows average absolute and incremental costs and effectiveness (quality-adjusted life years – QALYs) per person, and the corresponding incremental cost-effectiveness ratios (ICERs). It is evident that the “do nothing” strategy is less expensive but, at the same time, the least effective. Immunizing Italian elderly individuals with TIV would produce an incremental cost of €4.69 and an incremental benefit of approximately 4 hours (Δ QALY per person = 0.000381, i.e. ca 5,000 QALYs per total cohort) in perfect health. From the Italian National Healthcare Service (NHS) perspective, this investment would be advisable, given the ICER €12,305/QALY gained. When directly comparing TIV and MF59-TIV, the latter was demonstrated to be highly cost-effective with an ICER of €4,527/QALY. By contrast, two other competitors (ID-TIV and QIV) were dominated by MF59-TIV. The head-to-head comparison of MF59-TIV with non-vaccination was also highly cost-effective with an ICER of €10,750/QALY. Similarly, both ID-TIV and QIV were cost-effective compared with non-vaccination with ICERs of €11,960/QALY and €19,655/QALY, respectively.

One-way sensitivity analysis

In the one-way sensitivity analysis of MF59-TIV vs TIV, only few input parameters had a significant impact on ICER. The first parameter was TIV VE. When the lower limit estimate (34%) was used, TIV was dominated by MF59-TIV, while setting this parameter to the higher limit (73%) produced a diametrically opposite outcome in that TIV became a dominant strategy. The second parameter was MF59-TIV VE: at the maximum level ICER was €222/QALY, while at minimum levels it grew up to €119,477/QALY. Finally, vaccine price was able to largely change the outcome: at the minimal TIV price ICER became €24,479/QALY, while at the maximum acquisition cost of TIV, MF59-TIV was a dominant strategy.

The second deterministic analysis, i.e. MF59-TIV vs non-vaccination revealed a higher number of parameters able to influence the ICER in a substantial manner. These included: influenza attack rate, VE, vaccine price, administration cost,

and QALY loss due to influenza. However, the min-max variation of this parameters resulted in ICERs ranging in a plausible interval (from €5,104 to €19,358 per QALY gained), i.e. well below the threshold of €30,000/QALY.

Probabilistic sensitivity analysis (PSA)

Fig. 1 shows the acceptability curves of the four vaccines and the non-vaccination option. At the threshold of €30,000/QALY, MF59-TIV has the probability of 58.8% to be the best choice, ID-TIV – 25.5%, while TIV and QIV remained permanently excluded (i.e. dominated).

The comparison between MF59-TIV and TIV is illustrated in Fig. 2 with the CE plane. As illustrated, MF59-TIV remains cost-effective with an ICER below €30,000/QALY in 58.3% of simulations, exceeds €30,000/QALY only in 13.1%, and in 18.1% is dominant. MF59-TIV is dominated by TIV in the remaining 10.5% of cases.

The probabilistic sensitivity analysis (PSA) of the comparison between MF59-TIV and non-vaccination is shown in Fig. 3. In 80.9% of the simulations, MF59-TIV is below the threshold value while it exceeds this value in 17.3% of cases. In 1.8% of cases it is dominant.

The sensitivity analysis concludes that the results of the base case are robust.

Discussion

To the best of our knowledge, the present paper is the first study that compared all available alternatives for the immunization of Italian elderly individuals; even in the international context, a few studies used more than two competitors. Here we established the fact that MF59-TIV had the most favorable CE profile among all existing, commercially available alternatives for the elderly in Italy. Indeed, compared with non-vaccination, MF59-TIV was highly cost-effective: the ICER was €10,750/QALY, which is well below all existing thresholds. A universal substitution of TIV with MF59-TIV in the Italian elderly population is highly advisable, given the ICER of less than €5,000/QALY. At the same time, our analyses showed that, compared with MF59-TIV, the universal use of ID-TIV and QIV among the elderly would produce greater cost and decreased health benefits (i.e. MF59-TIV was dominant).

Our sensitivity analysis highlighted the robustness of the base case results. In particular, in the one-way simulation where MF59-TIV was compared with non-vaccination, no ICER estimates exceeded €30,000/QALY. When MF59-TIV was compared with TIV, it emerged that the VE of both

Table 1. Base case cost-effectiveness analysis of different seasonal influenza vaccination strategies among the Italian elderly population.

Strategy	Cost, €	Incremental cost, €	Effectiveness, QALY	Incremental effectiveness, QALY $\times 10^3$	ICER, €/QALY
Non-vaccination	6.23	—	8.960458	—	—
TIV	10.92	4.69	8.960839	0.381	12,305
MF59-TIV	11.35	0.43	8.960935	0.095	4,527
ID-TIV	11.54	0.19	8.960902	Negative	Dominated
QIV	14.21	2.86	8.960864	Negative	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; ID-TIV, intradermal trivalent inactivated vaccine; MF59-TIV, MF59-adjuvanted trivalent inactivated vaccine; QALY, quality-adjusted life year; QIV, quadrivalent inactivated vaccine.

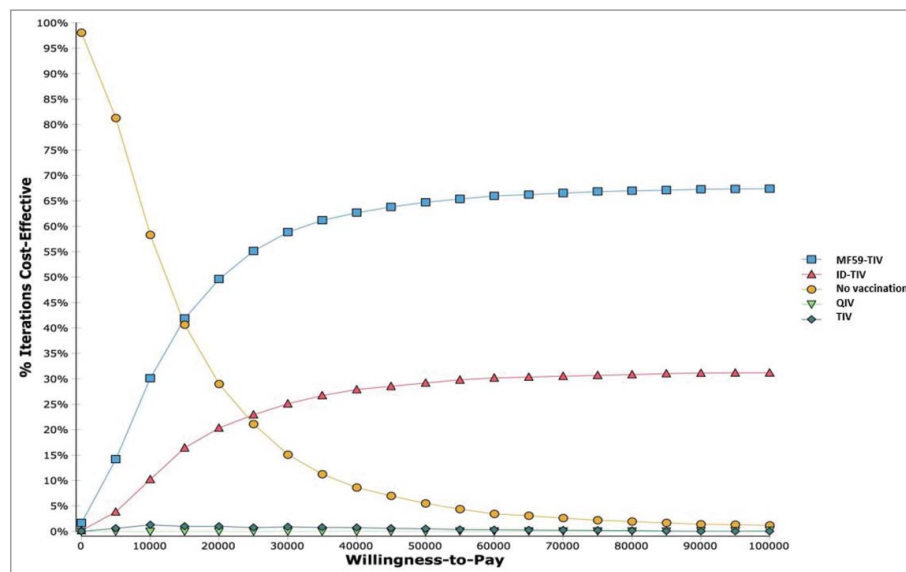


Figure 1. Cost-effectiveness acceptability curves of all five study strategies.

vaccines was the main driver of ICER. However, two points are noteworthy here. First, it is highly unlikely that TIV may have a greater VE than MF59-TIV since no study published so far has established the superiority of TIV over MF59-TIV in terms of both immunogenicity and effectiveness; by contrast, several meta-analyses^{10-13,25} have demonstrated MF59-TIV to provide better protection than non-adjuvanted TIV. Second, the relative VE of MF59-TIV of 25% adopted in the present analysis is likely to be an underestimate: a study by Van Buynnder et al.²⁶ demonstrated MF59-TIV to have a relative VE compared with TIV of 63% against laboratory-confirmed influenza.

While the univariate sensitivity analysis allows for the identification of the main drivers of the pharmacoeconomic outcome, it undoubtedly underestimates the uncertainty level around ICER since it assumes that this uncertainty is relative to only one parameter at one time. This shortcoming was addressed by PSA: MF59-TIV was cost-effective or cost-saving in 76% and 83% of simulations when directly compared with TIV and “do nothing”, respectively. These probabilities are very high. Indeed, it has been shown²⁷ that health technologies with at least 40% probability of being cost-effective in PSA tended to be recommended by the National Institute for Health and Care Excellence (NICE).

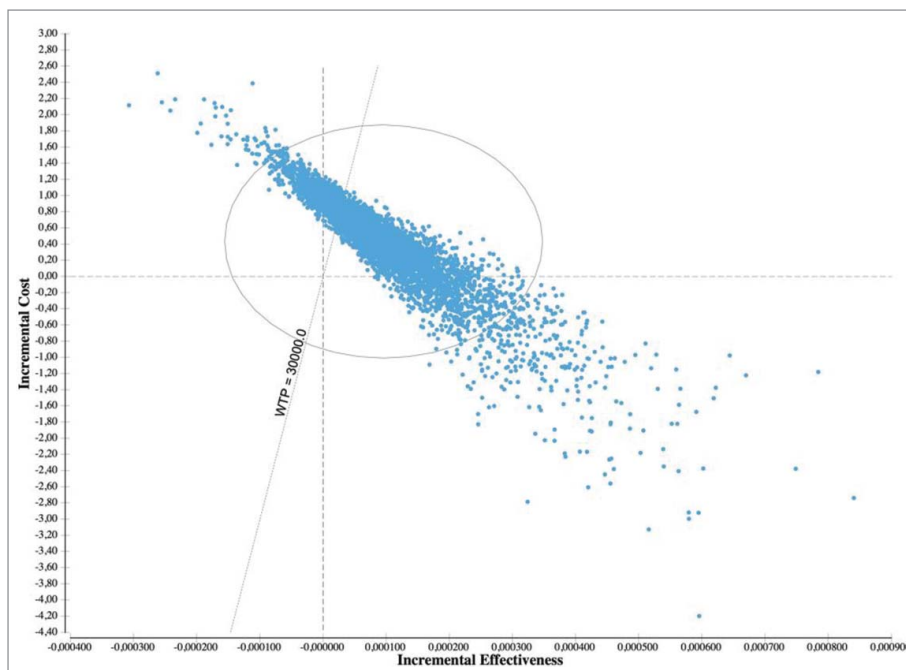


Figure 2. Cost-effectiveness plane of the probabilistic sensitivity analysis (10,000 rounds): MF59-adjuvanted trivalent inactivated vaccine (MF59-TIV) versus trivalent inactivated vaccine (TIV).

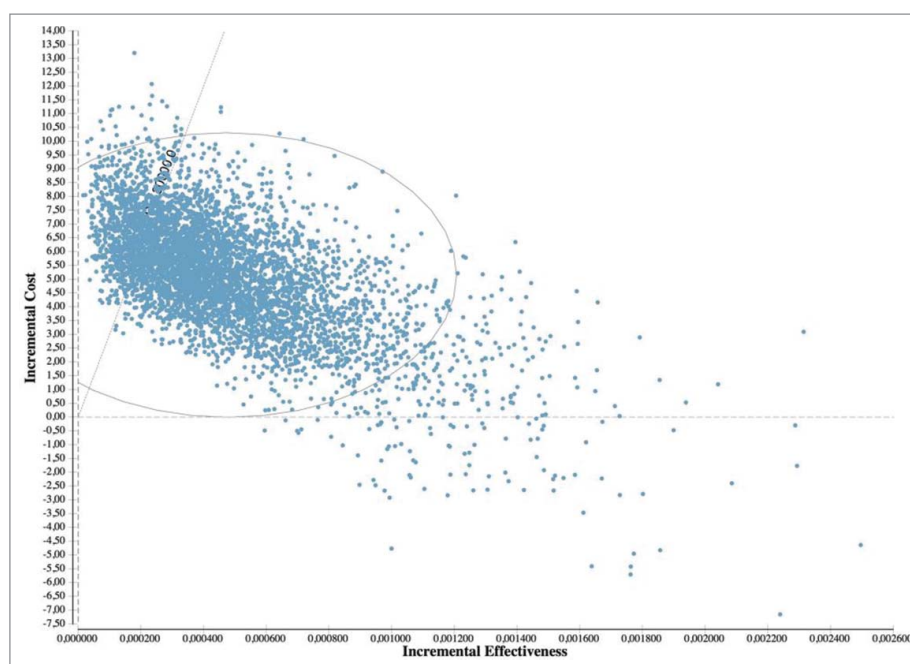


Figure 3. Cost-effectiveness plane of the probabilistic sensitivity analysis (10,000 rounds): MF59-adjuvanted trivalent inactivated vaccine (MF59-TIV) versus no vaccination.

The results of the present analyses should be compared with previously published Italian studies^{15,17}; however, these studies compared only two strategies, namely “MF59-TIV vs non-vaccination” and “MF59-TIV vs TIV”. Regarding these two strategies, our results are similar in that MF59-TIV is cost-effective. On the other hand, in the previous research MF59-TIV has been found not only to be cost-effective but also cost-saving compared with both TIV and “do nothing”. The explanation is likely to be connected to the model assumptions that were more conservative in the present analysis. For instance, here we used the laboratory-confirmed infection as influenza-related outcome, while the previous models used influenza-like illness (ILI) and other influenza proxies; given that the influenza node is in the beginning of the decision tree, all consecutive parameters like hospitalizations and deaths decreased substantially. Similarly, although we adjusted the hospitalization rate by the laboratory test sensitivity, this parameter may be still underestimated since only a small amount of the hospitalized elderly underwent laboratory assessment. In this regard, Reed et al.²⁸ have calculated that the observed number of influenza-related hospitalizations should be multiplied by a factor of 5.2.

If we consider international CE evaluations,^{14,16,18,20} our results still remain in a highly plausible range. A French model by Piercy et al.¹⁴ has demonstrated that the use of MF59-TIV instead of TIV among the high-risk elderly population is cost-effective, with however, some (sub)type variability in the ICERs (€17,496, €3,759 and €4,821 per life year gained for A/H1N1, A/H3N2 and B, respectively). In Canada, the substitution of TIV with MF59-TIV in the elderly was highly cost-effective (ICER = \$2,111/QALY).¹⁶ A more recent CE analysis by Mullikin et al.¹⁸ was conducted from the United States (US) perspective, where the universal seasonal influenza recommendation is in place. Their model compared various public health strategies, in which different vaccines were offered to different age categories. From these data, it

seems that the most attractive strategy would be the use of MF59-TIV among the elderly and QIV among the younger age groups. Finally, a very recent United Kingdom (UK) CE analysis²⁰ has reached similar results: MF59-TIV is cost-effective with an ICER of £3,540 (approximately €4,000/QALY), if used preferentially to current UK immunization practice among ≥ 65 -year-olds. The previous findings underline that our ICER estimates may be generalizable.

Particular attention should be paid to the use of the recently marketed QIV in the elderly. QIV is undoubtedly a further and important step towards a universal influenza vaccine. However, the relatively low impact of B type influenza in the Italian elderly population,²⁹ the suboptimal protection provided by non-adjuvanted vaccines^{10,30} and the relatively high acquisition cost,³¹ may have lowered the CE profile of QIV. We would like to discuss that our imputation approach to determine a relative advantage of the second B strain is likely to be overestimated in older adults for two reasons. First, we used in-house 13-season data on the distribution of types A and B among the elderly and these came from a single North Italian region. The selected parameter of 17.9% may have overestimated the national multi-season average of the relative frequency of type B among the elderly by as much as 3 times. Indeed, the Global Influenza B Study²⁹ has established that in Italy the average isolation rate of type B among seniors is only about 5%. Second, the assumed reduction of TIV VE may also be overestimated. The recent meta-regression analysis,³² that investigated both immunogenicity-derived estimates of VE and field VE, has documented that the impact of B lineage mismatch may be high in very young populations (up to 73%) but it is negligible in the elderly (about 3%). From the economic perspective, these thoughts are corroborated with a recently published UK CE analysis³³; this study shows that QIV may be cost-effective in all target groups. However, QIV may be cost-effective in children with an increased cost per dose of up to €6.36, while the program

extension to all elderly would admit an increase of only £0.20 per dose. Therefore, we believe that the current Italian market of influenza vaccines and tender policies should be differentiated according to the age of the target groups. In fact, in the US study by Mullikin et al.¹⁸ it has been established that the immunization strategy in which people below 65 years are vaccinated with QIV and the elderly with MF59-TIV is the most cost-effective. Considering that at the European level there is some tendency to extend the vaccination offer to other population groups^{34–36} and the fact that the price of QIV may drop in the near future, it will be useful to carry out a differentiated CE modeling approach like that of Mullikin et al.¹⁸

Another suggestion for future economic research resides in the modelling of co-administration of influenza and pneumococcal vaccines. This would be of relevance for Italian decision makers and other stakeholders given that the most recent 2017–2019 National Immunization Plan³⁷ explicitly recommends the pneumococcal vaccination for people aged 65 years and above. Indeed, these vaccines may provide a synergistic effect by further reducing numbers of hospitalizations and deaths³⁸ compared with strategies when administered alone. Clinical trials have suggested that both vaccines may be safely co-administered in different arms. For instance, the co-administration of MF59-TIV with either 13-valent pneumococcal conjugate vaccine (PCV-13)³⁹ or 23-valent pneumococcal polysaccharide vaccine (PPV-23)⁴⁰ did not produce any immunological inference or significantly increased reactogenicity. Given that both influenza⁶ and pneumococcal vaccines^{41,42} are highly cost-effective, the economic profile of their co-administration could be even more attractive.

Like all CE studies the present one is not without limitations that should be taken into account during the interpretation of our findings. In the previous paragraphs as well as in the “Methods” section we already discussed some issues around the underestimation of our input parameters; however, we actually consider these shortcomings to be study strengths, because we showed that each available influenza vaccine is cost-effective even at conservative assumptions (the authors favored a conservative approach). Possible study limitations include the fact that, some input parameters such as complications, hospitalizations and mortality following an influenza episode were not conducted in Italy but in the UK or US. The scoping review conducted during a health technology assessment (HTA) did not allow us to identify any Italian study that would have reported representative and robust data on the parameters of interest. However, we believe that the selected parameters may be applied to the Italian situation with a great confidence, since they came from relatively large studies and it is plausible to hypothesize that the clinical course of laboratory-confirmed influenza is similar in industrialized countries. In any case, the surrounding uncertainty was addressed by performing sensitivity analyses with adequate ranges. Second, our model considers an average VE and thus does not distinguish among single (sub)types. Piercy et al.¹⁴ have shown that MF59-TIV has the lowest ICER vs TIV in the case of the A/H3N2 subtype. This is highly plausible because A/H3N2, which has a relatively high mutation rate, causes the majority of the socio-economic influenza-associated burden in the elderly^{43,44} and MF59-TIV may provide significantly better protection against drifted A/H3N2 strains than TIV.²⁵ The recent statistical

estimation⁴⁵ of the (sub)type-specific relative VE has established that MF59-TIV may be more effective than TIV by 33%, 44%, 12% and 37%, 33%, 8% against A/H1N1, A/H3N2 and B homologous and heterologous strains, respectively. Considering these data and the fact that A/H3N2 is responsible for the majority of the influenza burden in the Italian elderly population,^{43,44} our input parameter of 25% is likely to be underestimated. And third (but not least), in the present study we adopted the third payer perspective that undoubtedly underestimates reality since it does not consider indirect costs. Although it is often considered that the elderly have a relatively low societal capital because most of them are retired, they may undoubtedly contribute to the reduction of indirect costs generated by influenza epidemics (e.g. grandparents look after grandchildren). This is particularly actual in the view in the “Healthy Ageing” initiatives undertaken throughout the world.

In conclusion, annual influenza vaccination dramatically reduces the burden of disease among the Italian elderly population; urgent actions should be undertaken in order to increase VC. From the economic perspective, it seems that MF59-TIV should be preferentially recommended to older adults in Italy.

Methods

Overview of the study objectives, model, outcome and reporting

The selection of model input parameters was driven by both systematic/scoping reviews conducted during a recently performed HTA of MF59-TIV⁴⁶ and expert opinion. Italy-specific data were always preferred providing that they were available and specific to and representative of the target population.

A novel decision tree model was constructed (TreeAge Pro 2017, TreeAge Software Inc.) in order to model the CE of different vaccination strategies among the Italian elderly. In order to reflect the National recommendations,⁴⁷ a cut-off of 65 years was used for the definition of the elderly. A total of five different strategies were compared: TIV, MF59-TIV, ID-TIV, QIV and non-vaccination. A stylized, simplified version of the decision tree is reported in Fig. 4. Briefly, every individual belonging to the low- or high-risk sub-cohorts (see below) that enters the model may receive either vaccine (according to the probability of being immunized) or no vaccination. The risk of contracting influenza will depend on both the baseline attack rate and vaccine type (i.e. VE). Influenza-positive subjects may develop complications treatable at either outpatient or inpatient regimens. In turn, the hospitalized patients may die or survive.

The study was conducted from the perspective of the Italian NHS. The time horizon was set to one year to reflect a single influenza season; for this reason, no discount rates were applied to costs. However, life expectancy for individuals entering the model was estimated in order to take into account benefits associated with deaths avoided due to vaccination. To do this, the loss of QALYs due to death was calculated by using the average life expectancy in Italy and age-specific utility for the elderly. The outcome of the model was the incremental cost per QALY gained (ICER); all costs were reported in 2017 Euros (€), while the measure of effects was expressed as QALYs.

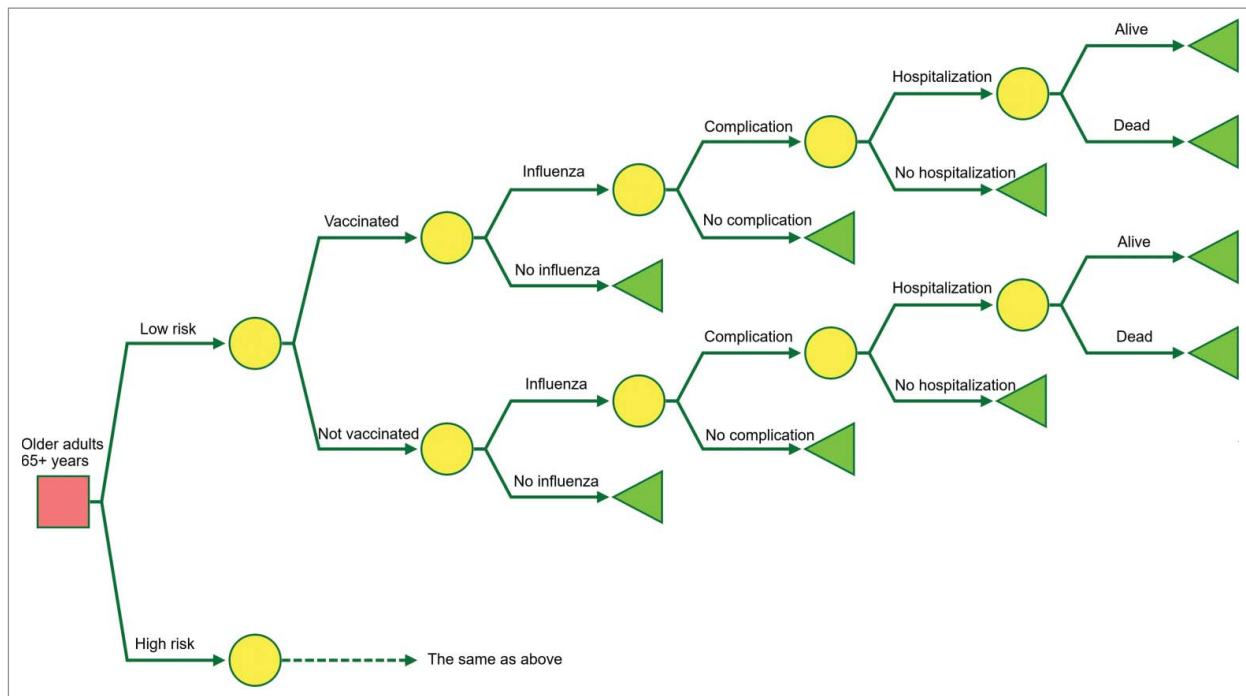


Figure 4. Simplified version of the decision tree.

The reporting is compliant with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.⁴⁸

Demographic, epidemiological and clinical input parameters

Study population. The target population included a cohort of Italian individuals aged 65 and above; the cohort size was 13,369,754 corresponding to 22% of the whole population.⁴⁹ Considering that the presence of underlying chronic conditions is a well-recognized^{50–53} risk factor for developing serious influenza-related complications and consequent hospitalizations, the whole cohort was split into two groups, namely “low-risk” and “high-risk”. The probability of belonging to low- and high-risk categories was set to 55.9% and 44.1%, respectively. These estimates derive from an elaboration of the National Institute of Statistics⁵⁴ that report the frequency of at least one serious chronic medical condition among people aged ≥ 65 years. The following chronic conditions are defined as serious: diabetes, myocardial infarction, angina pectoris, other cardiac diseases, stroke, intracerebral hemorrhage, chronic bronchitis, emphysema, cirrhosis, malignancies (including lymphoma and leukemia), parkinsonism, Alzheimer’s disease and dementia. Of note, the aforementioned chronicities are similar to the list of conditions (reported annually by the Italian Ministry of Health),⁴⁷ for which seasonal vaccination is recommended. Moreover, the estimates are in line with Italy-specific elaborations reported by Ryan et al.⁵⁵ and used in previous Italian economic evaluations.³¹ For the sensitivity analysis a variation of $\pm 20\%$ was considered plausible.

Vaccination coverage. To the best of our knowledge, nowadays there are no publicly available Italian population-based data on VC among the low- and high-risk elderly. However, it is unlikely that these two population groups have the same probability of being immunized. Indeed, the systematic review

by Yeung et al.⁵⁶ has highlighted that the presence of a chronic condition is an independent predictor of vaccine uptake. To find out risk-specific VC rates we proceeded as follows. First, an average VC of the last ten seasons (excluding the pandemic season) in the whole elderly population⁵⁷ was computed, being 59.9%. Then, we calculated an approximate 20% more chance to adhere to seasonal vaccination among the high-risk elderly.⁵⁸ Therefore, the risk-specific VCs were imputed by solving the following equation: $(P_{\text{low risk}} \times c) + [P_{\text{high risk}} \times (1.2 \times c)] = 59.9\%$, where c is VC among the low-risk elderly. This resulted in VC rates of 55.1% and 66.0% for the low- and high-risk elderly, respectively. To account for the between-season variability in VC, a variation of $\pm 20\%$ was used in the sensitivity analysis.

Laboratory-confirmed influenza attack rates. Similar to the previous parameter, we failed to identify the influenza attack rate (i.e. baseline risk) among non-vaccinated Italian elderly individuals from a single source. Therefore, the parameter was imputed using the following methodology. First, we used a meta-analytic estimate of 16.8% (95% CI: 6.6–33.1%) obtained through pooling of the ILI attack rate among the non-vaccinated Italian elderly.¹⁷ We then examined all available seasonal (seven consecutive seasons excluding the pandemic) virus isolation rates routinely collected by the Italian virological surveillance system Influnet.⁵⁹ On average, 32.1% of isolates from ILI patients were influenza positive. The probability of influenza was therefore computed as a product of ILI attack rate and average virus isolation rate, being 5.4% (range: 2.1–10.6%). It was assumed that the elderly at low and high risk for influenza complications have the same influenza attack rates. Our input parameter is also perfectly in line with the estimate of 5.7% derived from a meta-analysis of placebo arms in Randomized Controlled Trials (RCTs) enrolling the elderly and used in previous economic evaluations.⁶⁰

Influenza-related complications. A total of eight different complications [bronchitis, pneumonia, unspecified respiratory tract infection (URTI), otitis media, gastrointestinal (GI) bleeding, cardiovascular, central nervous system (CNS), and renal] attributable to influenza were considered (Table 2); their probabilities (both point estimates and 95% CIs) were extracted from Meier et al.⁵³

Care seeking and hospitalizations. The probability of care seeking during an ILI episode among Italian elderly individuals has recently been quantified by Perotta et al.⁶¹ These authors reported results of the 3-year activity of Influeweb, that is an online participatory surveillance platform for influenza. We estimated (by extracting data from a figure through WebPlotDigitizer)⁶² that on average (mean of 3 seasons, range 29–41%) 38.6% of Italian ≥ 65 -year-olds reported to seek medical service. Since we could not identify any Italian population-based study or surveillance system that would report elderly-specific data on hospitalizations due to laboratory-confirmed influenza and its complications, data from the US surveillance system FluSurv-NET⁶³ were adapted to the Italian situation. By averaging the available seasonal data on the cumulative hospitalization rate, it was possible to figure out a rate of 111.8 per 100,000 elderly people. By applying this rate to the target population, we could estimate a total of 14,947 expected hospitalizations among the Italian elderly. However, the number obtained is undoubtedly an underestimate for different reasons, including a relatively low probability of being tested for influenza in hospital and far from optimal polymerase chain reaction (PCR) test sensitivity among the elderly (on average 63.5%).⁶⁴ In order to partially address this issue, we applied the following correction formula: $N_{\text{hospitalizations corrected}} = N_{\text{hospitalizations expected}} \times 1/\text{Sensitivity}_{\text{PCR}}$.^{28,64} This resulted in 23,539 hospitalizations. Considering the attack rate of 5.4% and a likelihood of developing any influenza related-complication of 10.9%,⁵³ the probability of hospitalization for the whole elderly population would be 29.9%. To establish risk category-specific probabilities of hospitalization, we first assumed that, like in the case of complications,⁵³ the elderly at high risk have a 1.3-fold higher likelihood of being hospitalized. Then, we applied the formula $(P_{\text{low risk}} \times h) + [P_{\text{high risk}} \times (1.3 \times h)] = 29.9\%$, where h is risk of hospitalization among the low-risk

elderly, and figured out the estimates of interest (low-risk: 26.4%; high-risk: 34.3%). Again, a range of $\pm 20\%$ was retained adequate for the purpose of sensitivity analysis.

Influenza-related mortality. The probability of death following influenza is one of the most uncertain parameters in economic modelling since its estimates vary greatly among single observational studies.^{43,44,53,65,66} This high variability is linked to various factors, including study design and methodology, setting, timeframe and many others. The commonly cited inputs are based on the so-called “excess mortality” that, by using various statistical techniques, measures an excess number of deaths observed during an influenza season. However, such an approach has been criticized⁶⁷ for several reasons. Indeed, an increased winter mortality in the elderly is not uniquely determined by the influenza virus. For instance, the human respiratory syncytial virus (RSV), that often mimics influenza, causes a significant burden in different age-classes including the elderly.⁶⁸ The uncertainty is further amplified by the fact that large population-based studies usually do not stratify mortality data by vaccination status.

For all these reasons it was decided to adopt a conservative approach. First, it was assumed that people may die only in hospital. Then we identified the study by Arriola et al.⁶⁶ as a source of data since it explicitly reported mortality data among both vaccinated and non-vaccinated elderly individuals. In particular, they registered 23 deaths out of 600 hospitalized non-vaccinated people aged ≥ 65 years. Given that $>90\%$ of enrolled patients had at least one underlying medical condition, it was assumed that the reported probability of death (3.8%) would refer to the elderly at high risk. For the low-risk elderly, the parameter was deflated to 3.6%, by applying a correction factor derived from a ratio of the probability of death among low- and high-risk elderly reported by Meier et al.⁵³ The assumed parameters are consistent with mortality data following hospitalization among PCR-positive elderly demonstrated by Puig-Barberà et al.⁶⁹ For the sensitivity analysis we used the ranges of 1.2–11.2% and 1.2–12.2% for the low- and high-risk, respectively. The high limit was derived from Meier et al.,⁵³ while the low one was reduced by approximately 3 times considering the

Table 2. Demographic, epidemiological and clinical input parameters, by risk category.

Parameter (probability)		Low-risk elderly		High-risk elderly			Ref	
		Base case	Range		Base case	Range		
			Low	High		Low		High
Risk category		.5590	.4470	.6710	.4410	.3530	.5290	54
Vaccination coverage		.5510	.4410	.6610	.6600	.5280	.7920	57, 58
Baseline attack rate of influenza		.0540	.0210	.1060	.0540	.0210	.1060	17, 59
GP visit		.3860	.2900	.4100	.3860	.2900	.4100	61
Complication	Bronchitis	.0269	.0238	.0302	.0346	.0305	.0390	53
	Pneumonia	.0104	.0086	.0126	.0131	.0106	.0160	
	URTI	.0450	.0411	.0493	.0467	.0420	.0518	
	Cardiovascular	.0009	.0004	.0017	.0080	.0061	.0103	
	CNS	.0021	.0013	.0032	.0031	.0020	.0047	
	Renal	.0005	.0002	.0011	.0016	.0008	.0028	
	Otitis media	.0021	.0013	.0032	.0015	.0007	.0027	
	GI bleeding	.0066	.0051	.0084	.0066	.0049	.0087	
Hospitalization Complication		.2640	.2210	.3170	.3430	.2740	.4120	53, 63, 64
Death Hospitalization		.0360	.0120	.1120	.0380	.0120	.1220	53, 66

Abbreviations: CNS, central nervous system; GI, gastrointestinal; GP, general practitioner; URTI, unspecified respiratory tract infection.

ratio between the point estimate and high limit of the two groups. The relatively high range permitted us to partly address the uncertainty around the mortality and highlight changes in the economic outcome when considering epidemics of different severity.

Table 2 summarizes demographic, epidemiological and clinical input parameters used to populate the model.

Vaccine effectiveness

The average absolute (i.e. against no vaccination) VE of TIV against laboratory-confirmed influenza among the elderly was derived from the meta-analysis of Jefferson et al.,³⁰ being 58% (95% CI: 34–73%). It was assumed that ID-TIV, MF59-TIV and QIV have a greater VE than TIV (i.e. relative VE > 0%). Indeed, in their regression model, Coudeville et al.⁷⁰ estimated that the relative VE of ID-TIV vs TIV was 16.5% (95% CI: 12.7–20.1%). MF59-TIV has been found⁷¹ to be 25% (95% CI: 2–43%) more effective than TIV that produces an absolute VE of 72.5%. The latter estimate perfectly coincides with the absolute VE of MF59-TIV of 72% against laboratory-confirmed influenza among the Canadian community dwelling elderly observed by Van Buynder et al.²⁶

The relative advantage of QIV was imputed since, to the best of our knowledge, there was not any efficacy data of QIV in the elderly. The imputation procedure was similar to that reported earlier.³¹ The starting point was that of quantification of the frequency of B type isolates (both lineages) among the Italian elderly. From the *ad hoc* elaborated elderly-specific Lombardy data (from the Inter-University Research Center on Influenza, which is one of the National influenza surveillance networks), it was possible to establish an average (across 13 seasons) isolation rate of B strain virus of 17.9%. Then, by assuming an average level of B lineage mismatch of 60.1%³¹ and a relative efficacy of QIV vs TIV against the mismatched B lineage of 35%,^{72,73} it was possible to estimate, by weighting the above probabilities, a surplus in VE of QIV vs TIV of 3.8%. For the sensitivity analysis the range 58.0–64.3% was used since it would reflect hypothetical scenarios of complete B strain match and mismatch.

In other words, the number needed to vaccinate (NNV) in order to avoid one laboratory-confirmed influenza case in the Italian elderly (when the baseline attack risk is .054) was 32, 28, 26 and 30 for TIV, ID-TIV, MF59-TIV and QIV, respectively.

Costs

Considering the adopted Italian NHS perspective, only direct medical costs were taken into account; these are reported in Table 3. The acquisition costs of all vaccines considered ex-factory prices,³¹ while the cost of vaccine administration was set to €6.16.^{74,75} Costs relative to the outpatient treatment of influenza complications were adapted from Marchetti et al.⁷⁶ Given that in Italy the hospital care is financed according to diagnosis-related groups (DRGs), DRG reimbursement tariffs were considered the best choice for most complications requiring in-hospital treatment.^{31,77} In particular, we applied DRG tariffs for

Table 3. Cost parameter inputs used in the model.

Cost category	Cost, €	Ref
TIV ex-factory price ^a	5.35	31
MF59-TIV ex-factory price	6.99	
ID-TIV ex-factory price	6.99	
QIV ex-factory price	11.08	
Vaccine administration	6.16	75
GP visit	20.66	74
Outpatient treatment of complications (except for otitis media)	80	76
Outpatient treatment of otitis media	50	76
Bronchitis (DRG 097)	1,832	31, 77
Pneumonia (DRG 090)	2,291	31, 77
URTI (DRG 080)	4,422	31, 77
Cardiovascular complications (weighted mean DRGs)	3,544	17
Renal complications (DRG 316)	3,734	31, 77
CNS complications (weighted mean DRGs)	3,507	17
Otitis media (DRG 069)	1,247	31, 77
GI bleeding (DRG 175)	2,091	31, 77

^a The ex-factory price of TIV is a weighted (by the volume sold) average of the available brands in Italy.

Abbreviations: CNS, central nervous system; DRG, Diagnosis related group; GI, gastrointestinal; GP, general practitioner; ID-TIV, intradermal trivalent inactivated vaccine; MF59-TIV, MF59-adjuvanted trivalent inactivated vaccine; QALY, quality-adjusted life year; QIV, quadrivalent inactivated vaccine; URTI, unspecified respiratory tract infection.

bronchitis, pneumonia, URTIs, renal complications, otitis media and GI bleeding (DRGs 097, 090, 080, 316, 069 and 175, respectively). By contrast, given a multiplicity of clinical presentations, and therefore DRGs, of cardiovascular and CNS complications, we used the relative costs estimated by Iannazzo¹⁷ that are weighted by the frequency DRGs.

Disutilities

It has previously been estimated,^{78,79} through the use of a standardized tool, that the annual utility loss for an episode of influenza is .0078. Utility loss for bronchitis (.00904), pneumonia (.01041), URTIs (.00904), otitis media (.01382) and cardiovascular complications (.1) were extracted from Mullikin et al.,¹⁸ while disutilities for renal and CNS complications (.0337 and .0375 if treated in outpatients and inpatients regimens, respectively) from Rotheberg et al.⁸⁰

Sensitivity analysis

The head-to-head comparisons deemed cost-effective underwent the sensitivity analysis. Different techniques were carried out in order to verify robustness of the base case and identify the main drivers of ICERs. First, the one-way deterministic sensitivity analysis was carried out by altering (according the above-described ranges) single parameter inputs. Then, PSA, which allows to check the joint effect of uncertainty, with 10,000 Monte Carlo iterations was performed. In the PSA, beta distributions were associated to demographic, epidemiological and clinical features of influenza, while gamma distributions were associated to costs and disutilities.

Disclosure of potential conflict of interest

Preliminary data of this study were presented at ESWI influenza conference (Riga, 10–13 September 2017) by SC who received a travel grant from Seqirus srl.

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References

- Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. *Lancet Infect Dis*. 2007;7:658–66. doi:10.1016/S1473-3099(07)70236-0. PMID:17897608.
- Monto AS, Ansaldi F, Aspinall R, McElhaney JE, Montañó LF, Nichol KL, Puig-Barberà J, Schmitt J, Stephenson I. Influenza control in the 21st century: optimizing protection of older adults. *Vaccine*. 2009;27:5043–53. doi:10.1016/j.vaccine.2009.06.032. PMID:19559118.
- Grohskopf LA, Sokolow LZ, Broder KR, Olsen SJ, Karron RA, Jernigan DB, Bresee JS. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices – United States, 2016–17 influenza season. *MMWR Recomm Rep*. 2016;65:1–54. doi:10.15585/mmwr.rr6505a1. PMID:27560619.
- European Centre for Disease Prevention and Control. Seasonal influenza vaccination and antiviral use in Europe – Overview of vaccination recommendations and coverage rates in the EU Member States for the 2013–14 and 2014–15 influenza seasons. Stockholm: ECDC. 2016. Available from: <https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/Seasonal-influenza-vaccination-antiviral-use-europe.pdf> (Accessed 12 October 2017) 2016.
- Vaccines against influenza WHO position paper – November 2012. *Wkly Epidemiol Rec*. 2012;87:461–76. PMID:23210147.
- Ting EEK, Sander B, Ungar WJ. Systematic review of the cost-effectiveness of influenza immunization programs. *Vaccine*. 2017;35:1828–43. doi:10.1016/j.vaccine.2017.02.044. PMID:28284681.
- Barberis I, Martini M, Iavarone F, Orsi A. Available influenza vaccines: immunization strategies, history and new tools for fighting the disease. *J Prev Med Hyg*. 2016;57:E41–6. PMID:27346939.
- Treanor JJ. Clinical practice. Influenza vaccination. *N Engl J Med*. 2016;375:1261–8. doi:10.1056/NEJMcpl512870. PMID:27682035.
- O’Hagan DT, Ott GS, Nest GV, Rappuoli R, Giudice GD. The history of MF59[®] adjuvant: A phoenix that arose from the ashes. *Expert Rev Vaccines*. 2013;12:13–30. doi:10.1586/erv.12.140. PMID:23256736.
- Podda A. The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine. *Vaccine*. 2001;19:2673–80. doi:10.1016/S0264-410X(00)00499-0. PMID:11257408.
- Banzhoff A, Nacci P, Podda A. A new MF59-adjuvanted influenza vaccine enhances the immune response in the elderly with chronic diseases: Results from an immunogenicity meta-analysis. *Gerontology*. 2003;49:177–84. doi:10.1159/000069172. PMID:12679609.
- Beyer WE, Nauta JJ, Palache AM, Giezeman KM, Osterhaus AD. Immunogenicity and safety of inactivated influenza vaccines in primed populations: A systematic literature review and meta-analysis. *Vaccine*. 2011;29:5785–92. doi:10.1016/j.vaccine.2011.05.040. PMID:21624411.
- Domnich A, Arata L, Amicizia D, Puig-Barberà J, Gasparini R, Panatto D. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: A systematic review and meta-analysis. *Vaccine*. 2017;35:513–20. doi:10.1016/j.vaccine.2016.12.011. PMID:28024956.
- Piercy J, Ryan J, Megas F. Economic evaluation of MF59 adjuvanted vaccine against influenza in the high-risk elderly population in France. *J Med Econ*. 2004;7:1–18. doi:10.3111/200407001018.
- Baio G, Pammolli F, Baldo V, Trivello R. Object-oriented influence diagram for cost-effectiveness analysis of influenza vaccination in the Italian elderly population. *Expert Rev Pharmacoecon Outcomes Res*. 2006;6:293–301. doi:10.1586/14737167.6.3.293. PMID:20528523.
- Fisman DN, Tuite AR. Estimation of the health impact and cost-effectiveness of influenza vaccination with enhanced effectiveness in Canada. *PLoS One*. 2011;6:e27420. doi:10.1371/journal.pone.0027420. PMID:22110645.
- Iannazzo S. Pharmacoeconomic evaluation of the MF59-adjuvanted influenza vaccine in the elderly population in Italy. *J Prev Med Hyg*. 2011;52:1–8. PMID:21710816.
- Mullikin M, Tan L, Jansen JP, Van Ranst M, Farkas N, Petri E. A novel dynamic model for health economic analysis of influenza vaccination in the elderly. *Infect Dis Ther*. 2015;4:459–87. doi:10.1007/s40121-015-0076-8. PMID:26350238.
- Ruiz-Aragón J, Grande Tejada AM, Márquez-Peláez S, García-Cenoz M. [Estimate of the impact of influenza vaccination with adjuvant MF59 in population over 64 years for the National Health System: effects and costs]. *Vacunas*. 2015;16:6–11. doi:10.1016/j.vacun.2015.02.002.
- Nguyen VH, Kelly K, Mansi JA. UK health economic model demonstrates use of adjuvanted trivalent seasonal influenza vaccine in older adults to be highly cost-effective. Paper presented at: 6th ESWI Influenza Conference; 2017 Sep 10–13; Riga, Latvia.
- Council recommendation of 22 December 2009, on seasonal influenza vaccination. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:348:0071:0072:EN:PDF> (Accessed 12 October 2017) 2009.
- National Institute of Statistics (ISTAT). Demographic future of the country. Available from: <https://www.istat.it/it/files/2017/04/previsioni-demografiche.pdf> (Accessed 12 October 2017) 2017.
- Odono A, Chiesa V, Ciorba V, Cella P, Pasquarella C, Signorelli C. Influenza and immunization: A quantitative study of media coverage in the season of the “Fluad case”. *Epidemiol Prev*. 2015;39:139–45. PMID:26499432.
- Rémy V, Langeron N, Quilici S, Carroll S. The economic value of vaccination: why prevention is wealth. *J Mark Access Health Policy*. 2015;3. doi:10.3402/jmahp.v3.29284. PMID:27123187.
- Food and Drug Administration (FDA). FDA Advisory Committee Briefing Document. Fluad, seasonal adjuvanted trivalent influenza vaccine. Available from: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM461917.pdf> (Accessed 12 October 2017) 2015.
- Van Buynder PG, Konrad S, Van Buynder JL, Brodtkin E, Krajden M, Ramler G, Bigham M. The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly. *Vaccine*. 2013;31:6122–8. doi:10.1016/j.vaccine.2013.07.059. PMID:23933368.
- Adalsteinsson E, Toumi M. Benefits of probabilistic sensitivity analysis – a review of NICE decisions. *J Mark Access Health Policy*. 2013;1 doi:10.3402/jmahp.v1i0.21240. PMID:27226828
- Reed C, Chaves SS, Daily Kirley P, Emerson R, Aragon D, Hancock EB, Butler L, Baumbach J, Hollick G, Bennett NM, et al. Estimating influenza disease burden from population-based surveillance data in the United States. *PLoS One*. 2015;10:e0118369. doi:10.1371/journal.pone.0118369. PMID:25738736.
- Caini S, Huang QS, Ciblak MA, Kuszniarz G, Owen R, Wangchuk S, Henriques CM, Njouom R, Fasce RA, Yu H, et al. Epidemiological and virological characteristics of influenza B: results of the Global Influenza B Study. *Influenza Other Respir Viruses*. 2015;9:3–12. doi:10.1111/irv.12319. PMID:26256290.

30. Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev.* 2010;(2):CD004876. PMID:20166072.
31. Kheiraooui F, Cadeddu C, Quaranta G, Poscia A, Raponi M, de Waure C, Boccalini S, Pellegrino E, Bellini I, Pieri L, et al. [Health technology assessment of the quadrivalent influenza vaccine Flu-QIV (Fluarix Tetra)]. *QIIPH.* 2015;4. Available from: <https://www.ijph.it/pdf/2015-v4-n5.pdf> (Accessed 12 October 2017) 2015.
32. Beyer WEP, Palache AM, Boulfich M, Osterhaus ADME. Rationale for two influenza B lineages in seasonal vaccines: A meta-regression study on immunogenicity and controlled field trials. *Vaccine.* 2017;35:4167–76. doi:10.1016/j.vaccine.2017.06.038. PMID:28655451.
33. Thorrington D, van Leeuwen E, Ramsay M, Pebody R, Baguelin M. Cost-effectiveness analysis of quadrivalent seasonal influenza vaccines in England. *BMC Med.* 2017;15:166. doi:10.1186/s12916-017-0932-3. PMID:28882149.
34. de Lusignan S, Correa A, Ellis J, Pebody R. Influenza vaccination: in the UK and across Europe. *Br J Gen Pract.* 2016;66:452–3. doi:10.3399/bjgp16X686677. PMID:27563114.
35. Kassianos G, Blank P, Falup-Pecurariu O, Kuchar E, Kyncl J, De Lejarazu RO, Nitsch-Osuch A, van Essen GA. Influenza vaccination: key facts for general practitioners in Europe—a synthesis by European experts based on national guidelines and best practices in the United Kingdom and the Netherlands. *Drugs Context.* 2016;5:212293. doi:10.7573/dic.212293. PMID:27540408.
36. Rational for the lifetime vaccination calendar. Available from: https://www.sip.it/wp-content/uploads/2016/09/Calendario-per-la-vita-2016_.pdf (Accessed 12 October 2017) 2016.
37. Gazzetta Ufficiale della Repubblica Italiana. Piano Nazionale Prevenzione Vaccinale PNPV 2017–2019. GU Serie Generale n.41 del 18-2-2017. Available from: <http://www.gazzettaufficiale.it/eli/id/2017/02/18/17A01195/sg> (Accessed 15 February 2018) 2017.
38. Gilchrist SA, Nanni A, Levine O. Benefits and effectiveness of administering pneumococcal polysaccharide vaccine with seasonal influenza vaccine: an approach for policymakers. *Am J Public Health.* 2012;102:596–605. doi:10.2105/AJPH.2011.300512. PMID:22397339.
39. Song JY, Cheong HJ, Hyun HJ, Seo YB, Lee J, Wie SH, Choi MJ, Choi WS, Noh JY, Yun JW, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine and an MF59-adjuvanted influenza vaccine after concomitant vaccination in ≥60-year-old adults. *Vaccine.* 2017;35:313–20. doi:10.1016/j.vaccine.2016.11.047. PMID:27919632.
40. Song JY, Cheong HJ, Tsai TF, Chang HA, Choi MJ, Jeon JH, Kang SH, Jeong EJ, Noh JY, Kim WJ. Immunogenicity and safety of concomitant MF59-adjuvanted influenza vaccine and 23-valent pneumococcal polysaccharide vaccine administration in older adults. *Vaccine.* 2015;33:4647–52. doi:10.1016/j.vaccine.2015.05.003. PMID:25980426.
41. Boccalini S, Bechini A, Gasparini R, Panatto D, Amicizia D, Bonanni P. Economic studies applied to vaccines against invasive diseases: An updated budget impact analysis of age-based pneumococcal vaccination strategies in the elderly in Italy. *Hum Vaccin Immunother.* 2017;13:417–22. doi:10.1080/21645515.2017.1264827. PMID:27925845.
42. Boccalini S, Bechini A, Levi M, Tiscione E, Gasparini R, Bonanni P. Cost-effectiveness of new adult pneumococcal vaccination strategies in Italy. *Hum Vaccin Immunother.* 2013;9:699–706. doi:10.4161/hv.23268. PMID:23295824.
43. Rizzo C, Viboud C, Montomoli E, Simonsen L, Miller MA. Influenza-related mortality in the Italian elderly: no decline associated with increasing vaccination coverage. *Vaccine.* 2006;24:6468–75. doi:10.1016/j.vaccine.2006.06.052. PMID:16876293.
44. Rizzo C, Bella A, Viboud C, Miller MA, Rota MC, Salmaso S, Ciofi degli Atti ML. Trends for influenza-related deaths during pandemic and epidemic seasons, Italy, 1969–2001. *Emerg Infect Dis.* 2007;13:694–9. doi:10.3201/eid1305.061309. PMID:17553246.
45. Nguyen VH, Mansi JA. Estimating the efficacy of adjuvanted versus standard seasonal influenza vaccines in older adults based on anti-haemagglutinin antibody titres. Paper presented at: 6th ESWI Influenza Conference; 2017 Sep 10–13; Riga, Latvia.
46. Di Pietro ML, Poscia A, Specchia ML, de Waure C, Zace D, Gasparini R, Amicizia D, Lai PL, Panatto D, et al. [Health Technology Assessment (HTA) of the adjuvanted influenza vaccine in the Italian elderly]. *QIIPH.* 2017;6. Available from: <https://www.ijph.it/pdf/2017-v6-n9.pdf> (Accessed 15 February 2018) 2017.
47. Italian Ministry of Health. Control and prevention of influenza: recommendations for season 2016–2017. Available from: http://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&pdalministero&id=2654 (Accessed 12 October 2017) 2016.
48. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Value Health.* 2013;16:e1–5. doi:10.1016/j.jval.2013.02.010. PMID:23538200.
49. National Institute of Statistics (ISTAT). Population on Jan 1, 2016. Available from: <http://demo.istat.it/pop2016/index.html> (Accessed 12 October 2017) 2016.
50. Barker WH. Excess pneumonia and influenza associated hospitalization during influenza epidemics in the United States, 1970–78. *Am J Public Health.* 1986;76:761–5. doi:10.2105/AJPH.76.7.761. PMID:3717461.
51. Glezen WP, Decker M, Perrotta DM. Survey of underlying conditions of persons hospitalized with acute respiratory disease during influenza epidemics in Houston, 1978–1981. *Am Rev Respir Dis.* 1987;136:550–5. doi:10.1164/ajrcm/136.3.550. PMID:3631727.
52. Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. *Arch Intern Med.* 1998;158:1769–76. doi:10.1001/archinte.158.16.1769. PMID:9738606.
53. Meier CR, Napalkov PN, Wegmüller Y, Jefferson T, Jick H. Population-based study on incidence, risk factors, clinical complications and drug utilisation associated with influenza in the United Kingdom. *Eur J Clin Microbiol Infect Dis.* 2000;19:834–42. doi:10.1007/s100960000376. PMID:11152308.
54. National Institute of Statistics (ISTAT). 2014 annual report. Situation of the country. Available from: <http://www.istat.it/it/files/2014/05/Rapporto-annuale-2014.pdf> (Accessed 12 October 2017) 2014.
55. Ryan J, Zoellner Y, Gradi B, Palache B, Medema J. Establishing the health and economic impact of influenza vaccination within the European Union 25 countries. *Vaccine.* 2006;24:6812–22. doi:10.1016/j.vaccine.2006.07.042. PMID:17034909.
56. Yeung MP, Lam FL, Coker R. Factors associated with the uptake of seasonal influenza vaccination in adults: a systematic review. *J Public Health (Oxf).* 2016;38:746–53. PMID:28158550.
57. Italian Ministry of Health. Influenza vaccination coverage. Available from: http://www.salute.gov.it/imgs/C_17_tavole_19_allegati_itemAllegati_0_fileAllegati_itemFile_3_file.pdf (Accessed 12 October 2017) 2017.
58. National Institute of Health (ISS). Reports ISTISAN 13/9. Available from: http://www.iss.it/binary/publ/cont/13_9_web.pdf (Accessed 12 October 2017) 2013.
59. Influnet. Virological surveillance. Available from: <http://www.iss.it/flu/index.php?lang=1&anno=2017&tipo=13> (Accessed 12 October 2017) 2017.
60. Chit A, Roiz J, Briquet B, Greenberg DP. Expected cost effectiveness of high-dose trivalent influenza vaccine in US seniors. *Vaccine.* 2015;33:734–41. doi:10.1016/j.vaccine.2014.10.079. PMID:25444791.
61. Perrotta D, Bella A, Rizzo C, Paolotti D. Participatory online surveillance as a supplementary tool to sentinel doctors for influenza-like illness surveillance in Italy. *PLoS One.* 2017;12:e0169801. doi:10.1371/journal.pone.0169801. PMID:28076411.
62. Rohatgi A. WebPlotDigitizer. Available from: <http://arohatgi.info/WebPlotDigitizer/> (Accessed 12 October 2017) 2017.
63. Centers for Disease Control and Prevention (CDC). Laboratory-confirmed influenza hospitalizations. Disponibile su: <https://gis.cdc.gov/GRASP/Fluview/FluHospRates.html> (Accessed 12 October 2017) 2017.

64. Millman AJ, Reed C, Kirley PD, Aragon D, Meek J, Farley MM, Ryan P, Collins J, Lynfield R, Baumbach J, et al. Improving accuracy of influenza-associated hospitalization rate estimates. *Emerg Infect Dis.* 2015;21:1595–601. doi:10.3201/eid2109.141665. PMID:26292017.
65. Jansen AG, Sanders EA, Nichol KL, van Loon AM, Hoes AW, Hak E. Decline in influenza-associated mortality among Dutch elderly following the introduction of a nationwide vaccination program. *Vaccine.* 2008;26:5567–74. doi:10.1016/j.vaccine.2008.08.003. PMID:18722492.
66. Arriola CS, Anderson EJ, Baumbach J, Bennett N, Bohm S, Hill M, Lindgren ML, Lung K, Meek J, Mermel E, et al. Does influenza vaccination modify influenza severity? Data on older adults hospitalized with influenza during the 2012–2013 season in the United States. *J Infect Dis.* 2015;212:1200–8. doi:10.1093/infdis/jiv200. PMID:25821227.
67. Doshi P. Are US flu death figures more PR than science? *BMJ.* 2005;331. doi:10.1136/bmj.331.7529.1412.
68. Falsey AR, Walsh EE. Respiratory syncytial virus infection in elderly adults. *Drugs Aging.* 2005;22:577–87. doi:10.2165/00002512-200522070-00004. PMID:16038573.
69. Puig-Barberà J, Natividad-Sancho A, Trushakova S, Sominina A, Pisareva M, Ciblak MA, Badur S, Yu H, Cowling BJ, El Guerche-Séblain C, et al. Epidemiology of hospital admissions with influenza during the 2013/2014 Northern Hemisphere influenza season: results from the Global Influenza Hospital Surveillance Network. *PLoS One.* 2016;11:e0154970. doi:10.1371/journal.pone.0154970. PMID:27196667.
70. Coudeville L, Andre P, Bailleux F, Weber F, Plotkin S. A new approach to estimate vaccine efficacy based on immunogenicity data applied to influenza vaccines administered by the intradermal or intramuscular routes. *Hum Vaccin.* 2010;6:841–8. doi:10.4161/hv.6.10.12636. PMID:20930559.
71. Mannino S, Villa M, Apolone G, Weiss NS, Groth N, Aquino I, Boldori L, Caramaschi F, Gattinoni A, Malchiodi G, et al. Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. *Am J Epidemiol.* 2012;176:527–33. doi:10.1093/aje/kws313. PMID:22940713.
72. Tricco AC, Chit A, Soobiah C, Hallett D, Meier G, Chen MH, Tashkandi M, Bauch CT, Loeb M. Comparing influenza vaccine efficacy against mismatched and matched strains: A systematic review and meta-analysis. *BMC Med.* 2013;11:153. doi:10.1186/1741-7015-11-153. PMID:23800265.
73. DiazGranados CA, Denis M, Plotkin S. Seasonal influenza vaccine efficacy and its determinants in children and non-elderly adults: a systematic review with meta-analyses of controlled trials. *Vaccine.* 2012;31:49–57. doi:10.1016/j.vaccine.2012.10.084. PMID:23142300.
74. Gazzetta Ufficiale della Repubblica Italiana. Remunerazione delle prestazioni di assistenza ospedaliera per acuti, assistenza ospedaliera di riabilitazione e di lungodegenza post acuzie e di assistenza specialistica ambulatoriale. 28 Gennaio. 2013. Available from: http://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2013-01-28&atto.codiceRedazionale=13A00528&elenco30giorni=false (Accessed 15 February 2018) 2013.
75. Nomenclatore tariffario delle prestazioni aggiuntive, Accordo Collettivo Nazionale medici generici, 23 marzo. 2005. Available from: http://www.sisac.info/aree/www.sisac.info/resources/MEDICINA_GENERALE/ACN_testo_integrato.pdf (Accessed 12 October 2017) 2005.
76. Marchetti M, Kühnel UM, Colombo GL, Esposito S, Principi N. Cost-effectiveness of adjuvanted influenza vaccination of healthy children 6 to 60 months of age. *Hum Vaccin.* 2007;3:14–22. doi:10.4161/hv.3.1.3657. PMID:17245134.
77. Nuove tariffe DRG 2015. Available from: https://www.google.it/url?sa=t&trct=j&q=&esrc=s&source=web&cd=2&cad=rja&uact=8ved=0ahUKEwj41dJStr3WAhUL4mMKHdAnDDEQFggsMAE&url=http%3A%2F%2Fnormativasan.servizirl.it%2Fport%2FGetNormativaFile%3FfileName%3D5641_DGR2014_2989_AllB3_TariffeDRG2015.xls&usq=AFQjCNF9tYVqpNvA297MD61vHMNRayjSsA (Accessed 12 October 2017) 2015.
78. Baguelin M, Jit M, Miller E, Edmunds WJ. Health and economic impact of the seasonal influenza vaccination programme in England. *Vaccine.* 2012;30:3459–62. doi:10.1016/j.vaccine.2012.03.019. PMID:22446636.
79. van Hoek AJ, Underwood A, Jit M, Miller E, Edmunds WJ. The impact of pandemic influenza H1N1 on health-related quality of life: A prospective population based study. *PLoS One.* 2011;6:e17030. doi:10.1371/journal.pone.0017030. PMID:21399678.
80. Rothberg MB, Bellantonio S, Rose DN. Management of influenza in adults older than 65 years of age: Cost-effectiveness of rapid testing and antiviral therapy. *Ann Intern Med.* 2003;139:321–9. doi:10.7326/0003-4819-139-5_Part_1-200309020-00007. PMID:12965940.